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► **To cite this version:**

I. Castan-Laurell, C. Dray, P. Valet. The therapeutic potentials of apelin in obesity-associated diseases. *Molecular and Cellular Endocrinology*, 2021, 529, pp.111278. 10.1016/j.mce.2021.111278 . hal-04569524

HAL Id: hal-04569524

<https://ut3-toulouseinp.hal.science/hal-04569524v1>

Submitted on 22 Jul 2024

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The therapeutic potentials of apelin in obesity-associated diseases

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Abstract

Apelin, a peptide with several active isoforms ranging from 36 to 12 amino acids and its receptor APJ, a G-protein-coupled receptor, are widely distributed. However, apelin has emerged as an adipokine more than fifteen years ago, integrating the field of inter-organs interactions. The apelin/APJ system plays important roles in several physiological functions both in rodent and humans such as fluid homeostasis, cardiovascular physiology, angiogenesis, energy metabolism. Thus the apelin/APJ system has generated great interest as a potential therapeutic target in different pathologies. The present review will consider the effects of apelin in metabolic diseases such as obesity and diabetes with a focus on diabetic cardiomyopathy among the complications associated with diabetes and APJ agonists or antagonists of interest in these diseases.

Keywords: apelin, APJ, obesity, type 2 diabetes, energy metabolism, cardiomyopathy

1. Introduction

Apelin was firstly shown to be a peptide expressed in different cell types (Tatemoto et al. 1998; Read et al. 2019) before to be considered as an adipokine (Boucher et al. 2005). Apelin is generated from preproapelin, a 77-amino acid precursor that will be further processed into different active forms such as apelin-36, apelin-17, apelin-13, [pyr-1]-apelin-13 resulting from spontaneous cyclisation of the N-terminal glutamine and more stable than apelin-13. Apelin-17 and [pyr-1]-apelin-13 represent the predominant forms in plasma (Azizi et al. 2008; Zhen et al. 2013). Apelin was considered to be the only ligand of APJ (a G-protein-coupled receptor) until the discovery of Elabela a 54-amino acid peptide (also named Toddler or apela), few years ago (Chng et al. 2013; Pauli et al. 2014). So far, Elabela is poorly expressed in adipose tissue (Shin et al. 2017) or secreted by adipocytes and thus does not represent a potential adipokine. For this reason, Elabela functions will not be addressed in the present review. Since the apelin/APJ system is present in a large number of tissues or cells and thus involved in several physiological functions and physiopathological situations (for review see Marsault et al. 2019; Shin et al. 2017), we will focus on the role of apelin in obesity-associated diseases such as type 2 diabetes and diabetic cardiomyopathy with an update of the pharmacological tools available and tested in this context.

2. Regulation of apelin expression and secretion in adipose tissue

The first regulator of apelin expression and secretion reported in adipocytes was insulin. The expression of apelin in adipocytes but also the plasma concentrations are increased in various mouse models of obesity associated to hyperinsulinemia (Boucher et al. 2005). During fasting and after re-feeding in mice, the pattern of apelin expression and secretion in adipocytes follows insulinemia. Moreover, insulin treatment results in an increased apelin gene

expression and secretion in both adipocyte cell lines and human isolated adipocytes (Boucher et al. 2005). It has also been shown that apelin expression increased during adipogenesis (Boucher et al. 2005; Zhu et al. 2015). Since insulin, other factors have been revealed as positive regulators of apelin gene expression in adipocytes or adipose tissue such as growth hormone (GH) (Kralisch et al 2007), inflammatory factors TNF α (Daviaud et al. 2006) and lipopolysaccharide (Geurts et al. 2011). Common mechanisms have been described to induce apelin gene expression in adipocytes cell lines such as a PI3K-dependent pathway for insulin, TNF α and GH or MAPK activation for insulin and TNF α but divergences also exist (for example involvement of PKC in response to insulin but not TNF α) (Boucher et al. 2005; Daviaud et al. 2006). Over-expression of peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC1 α), a key regulator of cellular energy homeostasis in oxidative tissues has also been shown to increase apelin gene expression and secretion in human adipocytes (Mazzucotelli et al. 2008). On the other hand, negative modulators of apelin expression in adipocyte are scarce. Glucocorticoids and aldosterone treatment in 3T3-L1 cells decreased apelin mRNA levels through p38 MAPK activation (Wei et al. 2005; Jiang et al. 2013), (fig. 1).

Different studies have also reported the effect of dietary intakes on apelin gene expression in adipose tissue. Globally, in high-fat fed mice or rats apelin mRNAs are increased in adipocytes or adipose tissue (Dray et al. 2010; Garcia-Diaz et al. 2007) even if opposite results have also been reported (Hwangbo et al. 2017). Nevertheless, it is not known whether the fatty acids present in the diet, depending on their nature, have a direct effect on apelin production. To our knowledge, no studies have reported the effect of polyunsaturated fatty acid from the omega-6 family on apelin gene expression or secretion in adipose tissue. However, eicosapentaenoic acid (EPA), from the omega-3 family and lipoic acid (LA), a short-chain fatty acid with antioxidant properties, increased apelin gene expression in adipose

tissue of cafeteria diet-fed rats (Perez-Echarri et al. 2009) as well as in 3T3-L1 adipocytes (Lorente-Cebrian et al. 2010; Fernandez-Galilea et al. 2011). EPA treatment increased both apelin gene expression by a PI3K/Akt-dependent signaling and apelin secretion through post-transcriptional mechanisms in 3T3-L1 adipocytes (Lorente-Cebrian et al. 2010) whereas LA was shown to increase mainly apelin secretion through inhibition of AMPK (Fernandez-Galilea et al. 2011).

In humans, a caloric-restricted diet in obese patients decreased apelin gene expression in adipose tissue (Castan-Laurell et al. 2008; Krist et al. 2013). Apelin regulation by dietary intakes has been the subject of a systematic review (Yuzbashian et al. 2018). Recently, it has also been shown that in non-diabetic subjects, apelin gene expression in both visceral and subcutaneous adipose tissue was associated with foods exhibiting a high glycemic index but not total carbohydrates intake (Yuzbashian et al. 2019). Even if this study has some limitations, it underlines the impact of the quality and quantity of dietary carbohydrates on the regulation of apelin.

The effect of dietary intake on apelin expression has also been studied in others tissues. Apelin mRNAs are present in different nuclei of the hypothalamus including the paraventricular, arcuate and supraoptic nuclei involved in the control of behavioral, endocrine processes and energy homeostasis (Reaux et al. 2002). Hypothalamic apelin levels were found to be higher in HFD fed mice (Reaux-Le Goazigo et al. 2011). Increased apelin gene expression has also been reported in the heart left ventricle of HFD rats (Czarzasta et al. 2016). In skeletal muscle (soleus) of HFD fed mice, apelin gene expression was not modified compared to chow fed mice (Dray et al. 2010, Bertrand et al. 2013) but mice fed a HFD supplemented with EPA had higher muscular apelin gene expression compared to HFD mice (Bertrand et al. 2013). In addition both apelin expression and secretion were increased in C2C12 muscle cell line treated with various concentrations of EPA (Bertrand et al. 2013),

demonstrating that apelin could be also considered a myokine. However, apelin expression as well as apelin plasma concentrations decreased in muscle of aged mice and in differentiated myotubes of old compared to young donors (Vinel et al. 2018). Interestingly, exercise is able to increase apelin gene expression both in skeletal muscle and adipose tissue of type 2 diabetic rats (Kazemi and Zahediasl 2018) but decreased apelin expression was also reported after endurance training in soleus muscle of diabetic rats (Son et al. 2017). This discrepancy could be due to differences in the animal model used (streptozotocin-nicotinamide induced diabetes and Zucker rats respectively) and in the exercise protocol. In humans, exercise was shown to increase apelin mRNAs in skeletal muscle of obese subjects (Besse-Patin et al. 2013).

3. Apelin, obesity and type II Diabetes

In obese mice, as mentioned before, both apelin expression in adipose tissue and blood concentrations are increased, questioning the significance of such an increase during obesity and whether it could be associated to an apelin-resistant state. Transgenic mice overexpressing apelin exhibited a resistance against diet-induced obesity (Yamamoto et al. 2011). In contrast, apelin deficient mice (apelin $-/-$) had increased adiposity, higher plasma leptin levels and were insulin resistant. This phenotype was exacerbated in apelin $-/-$ mice fed a high-fat/ high-sucrose diet (Yue et al. 2010). It has also been reported that apelin $-/-$ mice fed a HFD display abnormal lymphatic and blood vessel enlargement that could participate to the development of obesity (adipocyte hypertrophy) through hyperpermeability to dietary fatty acid (Sawane et al. 2013). Altogether, these data are in favor of a positive role of apelin in metabolic diseases. High levels of apelin into the circulation might be helpful to delay or reduce insulin resistance in mice.

What do we know about the systemic effects of apelin on energy metabolism? We will focus mainly on *in vivo* studies. Acute apelin-13 treatment (intravenous administration) in normoponderal and obese/insulin resistant mice improves glucose tolerance and insulin sensitivity (Dray et al. 2008). Apelin was shown to stimulate glucose transport in skeletal muscle of non-obese mice in an AMPK-dependent manner (Dray et al. 2008). However, the study of Hwangbo et al; (2018) reported complementary information to explain apelin's glucose-lowering effect. They showed that apelin receptor was mainly expressed in endothelial cells (EC) of skeletal muscles or adipose tissue and that its specific deletion ($Aplnr^{ECKO}$ mice) resulted in glucose intolerance. Moreover, in skeletal muscle of $Aplnr^{ECKO}$ mice, apelin failed to activate AMPK compared to muscle with EC (Hwangbo et al. 2017) supporting the importance of EC signaling. Furthermore, expression of FABP4, a protein involved in fatty acid binding and transport as well as excess fatty acid accumulation was increased in skeletal muscles of $Aplnr^{ECKO}$ mice. Impaired glucose uptake in muscle of $Aplnr^{ECKO}$ mice could be rescued by FABP4 inhibition (Hwangbo et al. 2017). Thus, targeting endothelial signaling and fatty acid transport in skeletal muscle in response to apelin could also be considered as an innovative strategy to improve insulin sensitivity.

Long-term apelin treatment in obese and insulin resistant mice has also revealed beneficial effects on both glucose and lipid metabolism. Indeed, Higuchi et al showed that apelin treatment during fourteen days (daily intraperitoneal injection) in non-obese mice decreased the mass of several fat depots and their triglycerides content (Higuchi et al. 2007). In addition, apelin-treated mice exhibited increased rectal temperature and oxygen consumption without alteration of food intake, indicating that energy expenditure was enhanced (Higuchi et al. 2007). Chronic apelin treatment during 4 weeks (daily intraperitoneal injection) in obese and insulin resistant mice revealed that apelin-treated mice had higher lipids utilization, mainly due to increased lipid oxidation in skeletal muscles and increased mitochondrial biogenesis

without significant effect on body weight (Attané et al. 2012). Apelin treatment results *in fine* in an amelioration of insulin sensitivity in HFD mice (Attané et al. 2012). In addition, in the same animal model, decreased hepatic steatosis was observed in apelin-treated mice (Bertrand et al. 2018). In HFD fed diabetic Goto-Kakizaki rats, apelin treatment during 4 weeks exerts also beneficial effect on glycemia, insulin resistance and apelin was shown to be as protective as metformin (Li et al. 2018).

In addition to systemic apelin effects on energy metabolism, intracerebroventricular (icv) apelin injection was also shown to modulate glucose metabolism. Indeed, acute injection of a low dose of apelin in non-obese fed mice decreased glycemia whereas a high dose has an opposite effect in fasted mice (Duparc T et al. 2011). As mentioned in the previous chapter, hypothalamic apelin levels are increased in obese mice (Reaux-Le Goazigo et al. 2011) which could contribute to insulin resistance. Indeed, icv injection of a low dose of apelin in HFD fed mice has no more beneficial effect on glycemia and a high dose induced glucose intolerance (Drougard et al. 2014). However, exogenous apelin treatment in HFD mice seems to be able to counteract the central effect of apelin.

Metabolic effects of different apelin-36 variants have also been studied in obese mice by the use of an adeno-associated virus (AAV). Six weeks after AAV injection, mice expressing apelin-36 gained less weight and had lower glycemia than apelin-13 injected mice. A variant apelin-36(L28A) retains full metabolic activity but these effects were described to be independent of the canonical APJ signaling (Galon-Tilleman et al. 2017). A recent study provides evidence that apelin-36(L28A) could in fact bind to the apelin receptor and that it was a G protein biased apelin receptor agonist (Nyimanu et al. 2019).

Since apelin peptides are subjected to rapid enzyme degradation in the circulation and thus have a short half-life (less than 5 min), different analogs with long-lasting effects were

developed (for review see Fischer 2020; Read et al. 2019; Huang et al. 2018). Some of them were studied in a context of obesity or metabolic dysfunctions. O'Harte et al. have shown that HFD fed mice treated with acylated apelin-13 amide analogues during 28 days had reduced food intake and decreased body weight (O'Harte et al. 2017). Moreover, these apelin analogues reduced blood glucose, triglycerides concentrations as well as LDL-cholesterol and improved HbA1c concentrations in comparison to saline-treated HFD mice (O'Harte et al. 2018). Long-term administration of apelin analogues were also studied in db/db mice and their anti-diabetic properties were as effective as incretins mimetics (O'Harte et al. 2020). A recombinant protein by fusing the IgG Fc protein to apelin-13 (Fc apelin-13) with an estimated half-life of 33 hours, was also reported to improve liver steatosis, glucose tolerance without affecting food intake and body weight in HFD-induced obese mice (Wang et al. 2018). However, non-peptidic APJ agonists or small molecules are rarely tested in vivo on metabolism but rather on cardiac functions (see next chapter). Concerning APJ antagonists and metabolism, apelin F13A (replacement of the C-terminus phenylalanine by alanine in apelin13) was shown to inhibit the beneficial effects of apelin-13 in insulin resistant mice on glucose tolerance and muscle β -oxidation (Attané et al. 2012). More recently, the use of a fluorescence-based high-throughput screening allowed to identify protamine as a full antagonist with regard to G protein and β -arrestin-dependent intracellular signaling, able to decrease glucose tolerance in chow-fed mice (Le Gonidec et al. 2017).

Considering now the translation to human physiopathology, different studies have shown that apelin was increased in the circulation of obese and hyperinsulinemic patients. Cavallo et al (2012) found that type 2 diabetes but not type 1 diabetes was associated with increased serum apelin levels whereas Habchi et al (2014) showed that apelin concentrations were significantly higher in type 1 diabetic patients than in control subjects and even higher than in type 2 diabetic patients. Interestingly, a combined treatment of metformin and a dipeptidyl

peptidase-4 (DPP-4) inhibitor was superior to metformin monotherapy to increase plasma apelin levels in type 2 diabetic patients (Fan et al. 2015). However, in newly diagnosed and untreated type 2 diabetic patients apelin levels were reduced compared to healthy controls (Erden et al 2008). High levels of apelin were shown to be associated with decreased risk of development of type 2 diabetes in the general population (DESIR: a 9-year prospective study on the French population) (Castan-Laurell et al. 2020). Interestingly, a recent study dedicated to machine learning in order to early detect undiagnosed diabetic patients in Iran, revealed that fasting blood sugar, HbA1c, visfatin but also apelin were a subset of significant features and make the best discrimination between diabetic versus non-diabetic obese women (Lotfi et al. 2020). Apelin can thus be considered as a promising predicting biomarker for metabolic diseases.

Since the apelin/APJ system represents a promising therapeutic target towards insulin resistance/type 2 diabetes, the proof of concept of the influence of apelin administration on insulin sensitivity has been done in sixteen healthy non-diabetic human volunteers. During an hyperinsulinemic euglycemic clamp, apelin perfusion improved significantly insulin sensitivity without having side effects (Gourdy et al. 2018). To investigate the effects of apelin or apelin analogs in a large cohort of type 2 diabetic patients will be then the next challenge.

4. Apelin and diabetic cardiomyopathy

Among the complications associated with diabetes, this chapter will be dedicated to the role of the apelin/APJ system in myocardial dysfunctions, for other complications such as nephropathy or retinopathy see reviews (Hu et al 2016; Shin et al. 2017; Read et al. 2019). Hyperglycemia, hyperinsulinemia and metabolic diseases including cardiac insulin resistance

are starting points of diabetic cardiomyopathy. Then increased cardiac fibrosis and stiffness will appear and afterwards the first clinical indications of heart failure such as left ventricular (LV) hypertrophy, cardiac remodeling and diastolic dysfunction (for review see Jia et al. 2018). Apelin exerts several effects on the cardiovascular system, being of interest in a context of diabetic cardiomyopathy. Indeed, apelin has been described as a very potent inotropic agent in vitro and in vivo in normal and failing hearts (Szokodi et al. 2002; Berry et al. 2004; Maguire et al. 2009). Promising compounds such as a G protein biased small molecule apelin receptor agonist (CMF-019) was also shown to be a positive inotrope in vivo, increasing cardiac contractility in rats (Read et al. 2016) and apelin-17 analogs (Gerbier et al. 2016). Several studies have also shown that apelin has a short-lasting vasodilation in a nitric oxide (NO)-dependent manner and lowers blood pressure (for more details, see review Folino et al. 2015; Zhong J.C. et al. 2017). Clinical trials demonstrated that exogenous apelin injection induced NO-dependent arterial vasodilation in healthy volunteers (Japp et al. 2008) and increased cardiac output even in patients with heart failure (Japp et al. 2010; Barnes et al. 2013). Moreover, apelin improves insulin-stimulated vasorelaxation both in an endothelium-dependent and -independent manner and reduced angiotensin II-induced vasoconstriction in subjects with central obesity (Schinzari et al. 2017). Apelin could thus be beneficial to improve hemodynamic alteration related to insulin-resistance.

Many factors can contribute to cardiac fibrosis through cell proliferation, differentiation or extracellular matrix production. Apelin was first shown to decrease angiotensin II-induced fibrosis by inhibiting PAI-1 in mice (Siddiquee et al. 2011) but also through transforming growth factor β (TGF- β) pathway. One contributor to TGF- β activation is sphingosine kinase 1 (Sphk1) that induces cardiac fibroblasts proliferation. Apelin was shown to inhibit TGF- β -mediated fibrotic response in primary culture of mouse cardiac fibroblasts via SphK1-dependent mechanism (Pchejetski et al. 2012). In addition, in a mouse model of pressure

overload inducing cardiac fibrosis, chronic apelin treatment reduced myocardial fibrotic remodeling (Pchejetski et al. 2012). Recently, it has been reported that apelin through other mechanisms could also decrease fibrosis such as inhibition of TGF- β 1/smad2/ α -SMA pathway (Lv et al. 2020) or PI3K/Akt activity in order to attenuate oxidative stress in rats with myocardial infarction-induced heart failure (Zhong et al. 2020). Obese mice treated with the long-acting Fc-apelin (as described in chapter 1) exhibit higher cardiac output and decreased cardiac fibrosis compared to untreated mice in addition to benefits on glucose tolerance (Wang et al. 2018).

Different mechanisms could be involved in the progression of cardiac hypertrophy such as hypertension. One of the earliest in vivo study showed that chronic apelin treatment for 2 weeks in mice increased cardiac output without evidence of hypertrophy (Ashley et al. 2005). However, Scimia et al. (2012) demonstrated that APJ KO and apelin KO mice had different responses in a mouse model of sustained pressure overload by transaortic constriction (TAC). APJKO mice had reduced myocardial hypertrophy and heart failure whereas apelin KO mice presented clear signs of heart failure (Scimia et al. 2012). It was demonstrated that APJ could transduce a signal independently of apelin and was thus a bifunctional receptor sensitive to stretch via recruitment of β -arrestin (Scimia et al. 2012). Furthermore, in an elegant study, Parikh et al (2018) showed that after exposure to TAC, mice with a specific APJ deletion in the endothelium (APJ^{endo}^{-/-} mice) displayed decreased LV systolic function and increased wall thickness whereas mice with a deletion specific in the heart (APJ^{myo}^{-/-} mice) were protected. To note, APJ^{endo}^{-/-} and APJ^{myo}^{-/-} mice display normal heart size and function at baseline. This study reveals that APJ stretch transduction is mediated specifically by myocardial APJ and leads to hypertrophic response whereas apelin binding to APJ blunted stretch-induced hypertrophy induction (Parikh et al. 2018). In line with these results, apelin-13 encapsulation in liposomes nanocarriers resulting in sustained apelin release in the same mouse model

(TAC) was shown to alleviate LV hypertrophy and to attenuate pressure overload-induced cardiac dysfunction (Serpooshan et al. 2015). Altogether these studies underline the importance to avoid β -arrestin-dependent pathway to ameliorate cardiac hypertrophy. Interestingly, MM07 a biased agonist for APJ was shown to stimulate vasodilation and to have inotropic effect in rats as well as increasing in human forearm blood flow (Brame et al. 2015). MM07 preferentially stimulates the G-protein signaling without activating β -arrestin dependent pathways (Brame et al. 2015). Its effects on mechanical stretch will be of interest.

In mice fed a high-fat diet for 24 weeks, apelin treatment also during 2 weeks reduced heart weight, diastolic and systolic diameters and thus cardiac hypertrophy but also attenuated contractile dysfunction (Ceylan-Isik et al. 2013). One actor playing an important role during cardiac hypertrophy development is Sirtuin3 (sirt3), exclusively located in mitochondria and possessing deacetylase activity. Sirt3 plays different roles, such as activating enzymes that reduce ROS production (affecting cardiac hypertrophy) or being part of metabolic processes (for review, see Ansari et al. 2017). Several studies have shown that apelin ameliorates diabetic cardiomyopathy by increasing cardiac sirt3 expression and decreasing ROS formation (Li et al. 2013; Zeng et al. 2014). Moreover, in a mouse model of obesity and cardiac hypertrophy, apelin treatment for 4 weeks, increased sirt3 mRNA expression in cardiomyocytes and β -oxidation in a sirt 3-dependent manner (Alfarano et al. 2015). More recently, Zeng et al. showed that endothelial sirt3 was playing an important role in glucose uptake and transport to cardiomyocytes (Zeng et al. 2020) and that apelin-induced glucose uptake was decreased in endothelial cells from sirt3 deficient mice demonstrating a paracrine action of the endothelial sirt3-apelin axis in the regulation of cardiomyocyte glucose transporter (Zeng et al. 2020). Sirt3 is also essential for apelin-induced myocardial angiogenesis and autophagy in diabetes (Hou et al. 2015 a,b). It has also been shown that apelin overexpression in heart of db/db mice alleviates diabetic cardiomyopathy by increasing

vascular density via Sirt3 and increased Ang-1/Tie-2 and VEGF/VEGFR2 expression (Zeng et al. 2014). So through activation of sirt3 and by different mechanisms, apelin displays cardioprotective effects.

Concerning the regulation of blood apelin during such phenomena, it has been reported that in untreated hypertensive patients with LV hypertrophy, serum apelin were lower than those without LV hypertrophy (Ye et al. 2015). In patients with hypertension and type 2 diabetes, reduced blood apelin levels were found compared to healthy volunteers (Koval et al. 2018). In addition, patients with concentric LV hypertrophy had the lowest apelin levels (Koval et al. 2018). Apelin has been suggested as an important regulator of hypertension progression and a predictor to assess the prevalence of LV hypertrophy.

5. Concluding remarks:

Both metabolic and cardiovascular diseases are major health problems separately and together, since the incidence of heart failure is higher in diabetic patients compared non-diabetic patients (Jia et al. 2018). Among other well-known adipokines, apelin (acute and chronic treatment) has been shown to exert beneficial effects in the pathophysiology of the cardiovascular system and in type 2 diabetes in different animal models and in humans (figure 2). In addition, plasma apelin is a promising biomarker for the detection of impaired glucose homeostasis and increased risk of heart failure. Of course, more studies are needed, especially in humans, to confirm that targeting the Apelin/APJ system is more than favorable by considering effects on other functions or complications associated with diabetes. However, it is a major strength for apelin and apelin receptor agonists to act both on metabolic and cardiovascular diseases. In-depth knowledge of apelin signaling pathways has already allowed the emergence of compounds able to discriminate effects in favor to therapeutic

benefits but again, in vivo studies, integrating both metabolic and cardiovascular impacts will be crucial in the coming years. Also, a convenient way to administrate these compounds (oral versus intravenous injection) has to be considered in addition to long-lasting effects for future clinical trials.

Funding sources: This work was supported by INSERM.

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Legend of figures:

Figure 1: Exogenous factors and situations regulating apelin **gene** expression positively (green arrows) and negatively (red arrows) in adipose tissue.

Figure 2: Metabolic and cardiac effects of apelin or APJ agonists (↑ : increased and ↓ : decreased effect).

Figure 1:

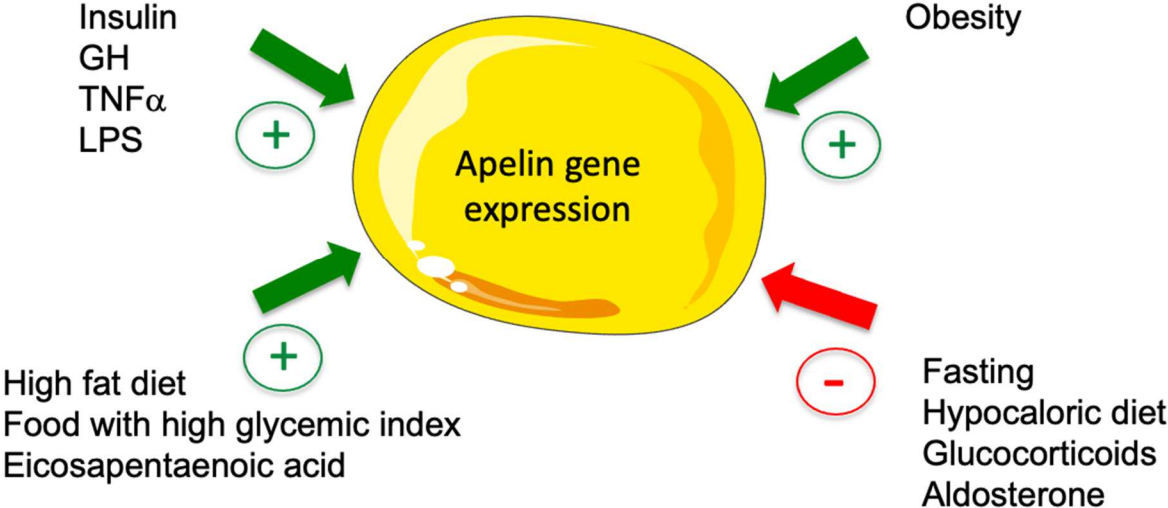


Figure 2:

